

down-regulating the expressions of IL-10 and TGF- β , anti-inflammatory cytokine, and promoting the IL-12 expression, pro-inflammatory cytokine. With HBV subunit vaccine, CIM can also enhance antigen specific cell-mediated response in animals.

The combination of LMS and CIM can synergistically enhance the immunogenicity of HBV subunit vaccine and leads to a robust at a comparative level achieved with CpG+alum in animals. Since the safety profile of the two chemicals, their combination with the HBV subunit vaccine may provide a cost effective and safe, yet effective therapy to treat those individuals chronically infected by HBV.

Concurrent Session 13 – Viral Hepatitis and Hepatocellular Carcinoma

I-64 Viral factors of hepatocellular carcinoma in chronic hepatitis B

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Chronic hepatitis B is the commonest cause of hepatocellular carcinoma (HCC) in Asia. Various clinical factors including older age, male gender, positive HBeAg and liver cirrhosis have been suggested to associate with a higher risk of HCC. Higher HBV DNA has been shown by various longitudinal studies to associate with a higher risk of liver cirrhosis and HCC. We have performed a longitudinal study comparing the serial HBV DNA among patients who developed and did not develop HCC. The trough HBV DNA level seemed to be the most important determinant of HCC development.

We have performed a prospective longitudinal study among 426 chronic hepatitis B patients with a follow-up up to 5 years. Genotype C HBV is found to be an independent risk factor of HCC over genotype B HBV. This is probably related to the more active liver disease and higher proportion of basal core promoter mutations related to genotype C HBV. In another study including 1006 patients followed up for over 7 years, HBV subgenotype Ce was found to associate with highest risk of HCC independent of HBV DNA levels.

To further investigate the virological mechanism of HCC by different HBV genotypes/subgenotypes, we have performed full genome sequencing of the HBV in 100 chronic hepatitis B patients with HCC and another 100 patients without HCC. Different viral genotypes and subgenotypes have different viral genomic markers for HCC. After data mining, algorithms can be derived with a sensitivity of HCC prediction of 70%–80%.

I-65 Hepatitis B and C viral-cellular interactions in the pathogenesis of hepatocellular carcinoma

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On a global scale, chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) account for well over 90% of hepatocellular carcinoma (HCC). Our Liver Research Center has been interested in viral-cellular protein interactions that may be responsible for this exceedingly high risk of hepatocyte transformation during persistent viral infection and how anti-viral agents may reduce this risk. There are two major signal transduction pathways that appear to be activated in most HCC and may occur very early in the disease process such as in dysplastic hepatocytes. The first is the insulin/IGF-1/IRS-1 signal transduction pathway involved in hepatocyte growth and survival. The

other major signaling pathway involves the Wnt/Frizzled/ β -catenin cascade involved in cell migration and proliferation normally “on” during embryonic development. However, aberrant activation of this pathway in adults can lead to tumor formation through its stimulatory effects on cell migration, invasion, and cell proliferation.

Finally, we will discuss recent reports that demonstrate interactions of HCV and HBV structural and non-structural proteins on various components of these two pathways that tend to promote activation during chronic viral infection. A further understanding of the interaction of viral and hepatocyte-derived cellular proteins will provide insights into the molecular mechanisms of HBV and HCV related HCC and begin to define the critical role of these interactions in the transformation process. These studies describe essential molecular mechanisms that may serve as targets for possible therapeutic intervention in addition to approaches that reduce viral replication and persistence via anti-viral agents.

I-66 How to predict HCC development in patients with chronic hepatitis B viral infection?

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Hepatocellular carcinoma (HCC) is one of the major malignant diseases in Asia. The incidence rates of HCC geographically differ according to high prevalence of hepatitis B virus (HBV) infection.

Chronic necro-inflammation by persistent HBV infection can progress to cirrhosis and meanwhile genetic changes can lead to the occurrence of HCC. Long standing inflammatory activities may play an important role in the clinical course of HBV infection. We studied 188 patients with chronic hepatitis B for a mean of 80.6 months to evaluate the long-term outcome of chronic hepatitis B patients, based on the histological grade and stage, in Korea. The development of cirrhosis correlated well with the grade of porto-periportal activity and stage of fibrosis ($p < 0.05$). Patients with a higher grade of porto-periportal activity and higher stage of fibrosis had a greater chance of developing cirrhosis. Based on ALT levels during follow-up, we classified the patients into active and inactive biochemical hepatitis groups. The probabilities of developing cirrhosis, decompensation, and HCC were significantly higher in the active biochemical hepatitis group ($p < 0.01$). Multivariate analysis showed that the prognostic factors for developing cirrhosis and decompensation were age and biochemical hepatitis activity during follow-up.

From our follow-up study, we can conclude that development of cirrhosis correlated well with the grade of porto-periportal activity and stage of fibrosis at liver biopsy. In addition, biochemical hepatitis activity during the follow-up was an independent prognostic factor affecting the long-term outcome of chronic hepatitis B. Therefore, effective control of hepatitis activity might improve the long-term outcome of chronic hepatitis B patients.

In high endemic areas of chronic HBV infection, a screening program to detect HCC development confined to the patients with chronic B viral liver disease is necessitated. The cost-effectiveness of a screening program could probably be increased further by focusing the screening of patients according to the risk factors most likely to affect them. Therefore, it is very important to assess the risk factors of HCC development. We demonstrated that the more risk factors, the higher HCC development. A tailored screening system with individual prediction model for HCC was also proposed based on relative significance of risk factors and prospectively confirmed. Recent our study of 688 patients with chronic B viral liver diseases